Development and validation of a non-invasive biomarker-based model to identify endoscopic recurrences of Crohn's disease

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Abstract

Background: Endoscopic recurrence is common in postoperative patients with Crohn's disease (CD). Monitoring endoscopic recurrence is important for selecting an appropriate treatment to prevent the development of postoperative disease. The aim of this study was to develop and validate a diagnostic model to identify endoscopic recurrence.

Methods: This was a retrospective cohort study recruiting postoperative CD patients who underwent endoscopy at the First Affiliated Hospital, Sun Yat-sen University from January 2016 to June 2020. Endoscopic recurrence was defined as Rutgeerts score > i1. Thirty non-invasive biomarkers, including C-reactive protein, erythrocyte sedimentation rate, vitamin D, complete blood count, and biochemical blood indices, were used as candidate predictors to build a multivariate logistic regression diagnostic model. The predictive ability of the diagnostic models was assessed by receiving the area under the characteristic curve (AUC) and calibration plots, and internal validation was performed by the bootstrap method.

Results: Two hundred and nineteen eligible patients were included in this study, and 135 (61.6%) patients had a postoperative endoscopic recurrence. The final diagnostic model included eight biomarkers with an AUC (95% confidence interval (CI)) of 0.796 (0.737–0.855) to identify endoscopic recurrence. The AUC, sensitivity, and specificity of this diagnostic model were 0.781 (0.780–0.782), 0.647 (0.643–0.651) and 0.811 (0.807–0.815), respectively, by internal validation. In addition, the diagnostic model exhibited good calibrability with calibration slope, calibration-in-the-large ('mean calibration') and Brier scores of 1.00, 0.00, and 0.175, respectively.

Conclusion: This non-invasive biomarker-based diagnostic model has an excellent ability to identify endoscopic recurrence in patients with CD. Application of the model to clinical practice to monitor postoperative patients may be helpful for patient management.

Keywords: biomarkers, Crohn's disease, endoscopic recurrence, predictive model

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Introduction

Crohn's disease (CD) is chronic and recurrent.[1] Despite substantial advances in medical treatment, approximately half of patients with CD still require bowel resection to treat complications or resistance to medical therapy.[2] However, bowel resection is not a cure, and disease recurrence is almost inevitable.[3,4] One year after, 70–90% of patients develop inflammatory lesions with endoscopic evidence of recurrence. In contrast, clinical evidence of recurrence is delayed, and only one-third of patients will develop severe disease symptoms 3 years after surgery.[5,6] Importantly, endoscopic recurrence is now considered to be

strongly associated with reoperation and poor prognosis in patients with CD.[7,8]

After surgery, ileocolonoscopy is considered the reference standard for regular monitoring of post-operative endoscopic recurrence and disease progression.[9] However, endoscopy is invasive, time-consuming, and always unpleasant for the patient, so there has been an active search for reliable and straightforward non-invasive markers. Fecal calprotectin (FC) and, radiology and imaging, such as ultrasound, magnetic resonance, and computed tomography, are less invasive, emerging alternatives for identifying postoperative recurrence and have been evaluated as independent correlates of endoscopic severity.[8,10–12] However, typical FC values vary by laboratory, and radiological, and imaging results overly depend on examiner experience.[13] Therefore, stable and accurate non-invasive methods are needed to identify endoscopic recurrences.

Hematologic indicators are readily available and stable. The main aim of this study was to develop and validate a hematologic biomarker-based diagnostic model to identify endoscopic recurrence in postoperative patients with CD that reliably reflects the severity of endoscopic presentation and facilitates the decision to select appropriate asymptomatic patients for endoscopic evaluation.

Methods

Study design and patient selection
This research was a retrospective single-center cohort study conducted at the First Affiliated Hospital, Sun Yat-sen University and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (the STROBE checklist is as shown in Supplementary Table 1).[14] The study was approved by the Institutional Review Board and Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University [2021(355)]. Patients with CD who met the inclusion and exclusion criteria and underwent endoscopy at this hospital between January 2016 and June 2020 were consecutively recruited for this study. Inclusion criteria included: (1) a precise diagnosis of CD based on clinical manifestations, endoscopy, and histological presentation; (2) age 18 years or older; (3) history of ileocolic resection; and (4) available data on c-reactive protein (CRP), serum

1,25-OH vitamin D, complete blood cell count, or biochemical markers [albumin, globulin, bilirubin, sodium, potassium, chloride, carbon dioxide, glucose, urea, creatinine, anion gap, aspartate aminotransferase (AST), alanine aminotransferase, alkaline phosphatase] within one week before and after the endoscopic procedure. Exclusion criteria included: (1) concurrent infection, gastrointestinal bleeding, or pregnancy; (2) over 50% missing data; and (3) intestinal strictures that prevented endoscopic access to the anastomosis and neo-terminal ileum (Figure 1).

Participant demographic and clinical characteristics, including age at endoscopy, sex, age at diagnosis, disease location, disease behavior, disease duration, and treatment received, were collected at the time of endoscopy. Disease location and disease behavior were recorded according to the Montreal classification.[15]

Definition of endoscopic recurrence
Two investigators independently assessed all endoscopic presentations according to the Rutgeerts score.[7] i0, no lesions; i1, fewer than or equal to five aphthous lesions; i2, over five aphthous lesions with normal intervening mucosa or lesions at the ileocolonic anastomosis; i3, diffuse aphthous ileitis with diffuse mucosal inflammation; i4, diffuse inflammation with large ulcers, nodules, and/or stenosis. In case of disagreement, the two investigators will discuss and then finalize Rutgeerts score. Endoscopic recurrence was defined as a Rutgeerts score $\geq$ i2. Endoscopic remission was defined as a Rutgeerts score equal to i0 or i1.

Non-invasive biomarkers
Thirty non-invasive biomarkers composed of serum CRP, erythrocyte sedimentation rate (ESR), serum vitamin D, complete blood cell count (white blood cell (WBC), neutrophil, lymphocyte, monocyte, eosinophils, red blood cell (RBC), hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentrate, platelets, thrombocytocrit, mean platelet volume), and biochemical blood indices (albumin, globulin, bilirubin, sodium, potassium, chloride, carbon dioxide, glucose, urea, creatinine, anion gap, = AST, alanine aminotransferase, alkaline phosphatase) were used as candidate predictors and participated in model
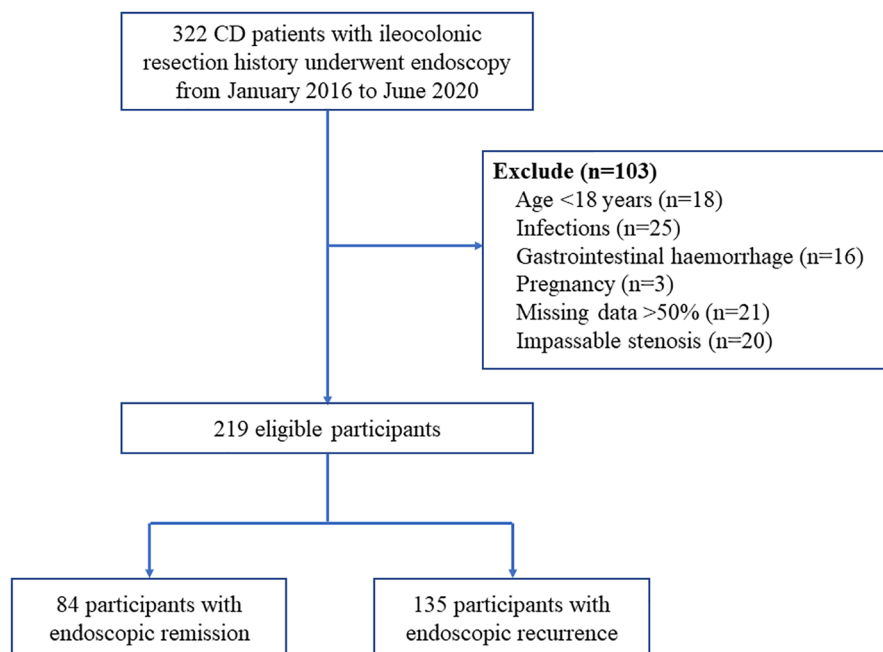
Figure 1. Flow chart of participants in this study.

development. Fecal calprotectin was not considered a predictor due to missing values in over 50% of participants. The testing of these non-invasive biomarkers was performed by the Department of Medical Laboratory of the First Affiliated Hospital, Sun Yat-sen University.

Missing values
Missing values for non-invasive biomarkers were resolved by simple imputation, as the proportion of missing values was very small (Supplementary Table 2). The single imputation data set was created as the first series of the multiple imputation data sets. The multiple imputation model included all non-invasive biomarkers and outcomes performed by the mice package in *R* (multiple imputation and number of iterations equal to 5 and 100, respectively).

Model development and internal validation
We implemented a three-step procedure to select non-invasive biomarkers involved in the diagnostic model. First, we selected three biomarkers (CRP, vitamin D, and platelets) based on previous studies and clinical experience. High CRP and low vitamin D levels have been associated with endoscopic recurrence.[13,16] In addition, CRP and platelets play an essential role in assessing endoscopic activity in patients with CD.[17,18] Therefore, these biomarkers were included in the first step of the diagnostic model. Next, backward exclusion was performed according to the Akaike information criterion to further select predictors. Five biomarkers (ESR, albumin, AST, WBC, and RBC) with *p*-values less than 0.1 in the backward logistic regression model were included in the diagnostic model (Supplementary Table 3). Third, we implemented a collinearity test among the eight biomarkers selected for the above procedure. No collinearity was observed among the eight biomarkers (Supplementary Table 4), so all biomarkers were included in the final model. Finally, a multivariate logistic regression model incorporating CRP, vitamin D, platelets, ESR, albumin, AST, WBC, and RBC was developed to identify endoscopic recurrence.

Using 1000 repetitions of the bootstrap procedure was for internal validation, and the mean and 95% confidence interval (CI) of the test performance, including the area under the receiver characteristic curve (AUC), sensitivity and specificity, were calculated.

Statistical analysis

Median (interquartile range, IQR) and frequency (percentage) were used for the statistical description of continuous and categorical variables, respectively. Univariate analysis between all non-invasive biomarkers and endoscopic recurrence was performed by binomial logistic regression and is shown as odds ratio (OR) with their 95% CI. The p-values < 0.05 were considered statistically significant. We did not perform sample size calculations but used the entire data set of all eligible samples for model development and internal validation. The sample size of our study was sufficient for model development according to the principle of '10 events per variable'. Predictors that selected through the aforementioned 'three-step procedure' were put into a binary logistic regression analysis to build up a multivariate prediction model (the diagnostic model). The β coefficients and ORs (95% CI) of all the predictors in this multivariate prediction model would be showed. We assessed the discrimination of the diagnostic model by AUC. The calibration of the model was assessed by calibration plots, calibration intercepts, and calibration slopes. The diagnostic model divided patients into two groups (endoscopic recurrence or endoscopic remission) by cutoff values, determined according to the Youden index. The sensitivity and specificity of the diagnostic model were then calculated. All statistical analysis was performed with R version 4.0.0.

Results

Patient characteristics

Two hundred nineteen patients met the inclusion and exclusion criteria in this study (Table 1). One hundred and thirty-five (61.6%) patients were diagnosed with postoperative recurrence by endoscopy. The median (IQR) age of patients at diagnosis and age at endoscopy were 31.7 (24.7–44.6) and 34.0 (27.8–47.0) years, respectively. One hundred forty (63.9%) patients were male. The median (IQR) time interval between the CD-related surgery and endoscopy procedure was 707 (304–1520) days. According to disease location, 26 (11.9%), 7 (3.2%), 186 (84.9%), 47 (21.5%), and 109 (49.8%) patients had ileal, colonic, ileocolonic, upper gastrointestinal, and perianal diseases, respectively. In addition, 59 (26.9%) and 160 (73.1%) patients suffered from stricturing and penetrating disease, respectively. In addition, 64 (29.2%) patients received thiopurine therapy, and 110 (50.2%) patients received anti-tumor necrosis factor antibodies at the time of endoscopy procedure.

Continuous variables are expressed as medians (interquartile spacing); categorical variables are expressed as frequencies (%).Non-invasive biomarkers associated with endoscopic recurrence

Univariate logistic regression analysis was performed between 30 candidates' non-invasive biomarkers and endoscopic recurrence, and the results are presented in Supplementary Table 5. Twelve biomarkers, including CRP, vitamin D, ESR, albumin, bilirubin, urea, AST, alanine aminotransferase, hemoglobin, mean corpuscular hemoglobin concentrate, platelets, thrombocytocrit, and mean platelet volume were significantly associated with endoscopic recurrence in both the original data set and the simple imputed data set. The levels of CRP [OR (95% CI) 1.07 (1.03–1.11), $p = 0.001$], ESR [OR (95% CI) 1.04 (1.03–1.06), $p < 0.001$], platelets [OR (95% CI) 1.01 (1.00–1.01), $p < 0.001$], and thrombocytocrit [OR (95%) (8.41–10,870.01), $p = 0.003$] were elevated in patients with endoscopic recurrence, while vitamin D [OR (95%) (0.89–0.97), $p = 0.002$], albumin [OR (95%) (0.83–0.94), $p < 0.001$], and AST [OR (95%) (0.90–0.97), $p < 0.001$] concentrations were reduced.

Diagnostic model of endoscopic recurrence

After a three-step predictor selection process (Figure 2), a diagnostic model containing CRP, vitamin D, platelets, ESR, albumin, AST, WBC, and RBC was developed. The regression coefficients and intercepts of each predictor in the diagnostic model are listed in Table 2. The logistic regression model for identifying endoscopic recurrence can be expressed as follows.

$$\text{probability}_{ER} = \frac{1}{1 + exp \begin{pmatrix} -0.018 + 3.54\ \text{CRP} \\ -3.37\ \text{vitamin D} \\ +0.034\ \text{platelet} \\ +2.75\ \text{ESR} - 1.88\ \text{albumin} \\ -4.5\ \text{AST} \\ -21.7\ \text{WBC} + 48.3\ \text{RBC}) \times 10^{-2} \end{pmatrix}}$$

where the probability$_{ER}$ shows the probability of endoscopic recurrence of the patient.

Performance of the diagnostic model

The diagnostic model have an AUC (95% CI) of 0.796 (0.737–0.855) for the discrimination of endoscopic recurrence (Table 3). In patients with different disease location, the diagnostic model have distinct AUCs to distinguish endoscopic recurrence (Supplement Figure 1). The mean and 95% CI AUC, sensitivity, and specificity of the model for identifying endoscopic recurrence were 0.781 (0.780–0.782), 0.647 (0.643–0.651), and 0.811 (0.807–0.815), respectively, as validated by internal bootstrapping. In addition, the diagnostic model exhibited good calibration with calibration slope, calibration-in-the-large and Brier score of 1.00, 0.00, and 0.175, respectively (Figure 3).

Discussion

This study aimed to develop and validate a model comprising non-invasive biomarkers to identify postoperative recurrence in CD patients. Thirty non-invasive biomarkers were used as potential candidates for the model, and they were screened in a three-step process. Finally, the predictive power of the model was assessed by internal validation. In summary, eight non-invasive biomarkers containing CRP, vitamin D, platelets, ESR, albumin, AST, WBC, and RBC were selected to develop a multivariate logistic regression model to identify postoperative recurrence in CD patients.

Postoperative patients with CD are challenging to manage because of their complex disease course, multiple symptomatic confounders, and poor sensitivity to treatment.[19] Management focuses on identifying patients with postoperative recurrence, as postoperative recurrence frequently occurs in CD patients, and a high-quality trial has shown that proactive therapy adjustment is better than the standard treatment.[20] How to identify patients with postoperative recurrence to adjust their treatment has become an urgent issue. Currently, monitoring strategies and treatment adjustments rely on early endoscopy 6–12 months after surgery, and the Rutgeerts' score has been developed to estimate postoperative recurrence in CD.[8] In addition, the most recent longitudinal follow-up of postoperative patients showed that

Table 1. Patient characteristics in the study cohort.

Characteristics	Participants (*n* = 219)
Male	140 (63.9)
Age at endoscopy procedure, years	34.0 (27.8–47.0)
Age at diagnosis, years	31.7 (24.7–44.6)
Time interval between surgery and endoscopy procedure, days	707 (304–1520)
Disease location	
L1 (ileal)	26 (11.9)
L2 (colonic)	7 (3.2)
L3 (ileocolonic)	186 (84.9)
L4 (upper gastrointestinal)	47 (21.5)
Perianal disease	109 (49.8)
Disease behavior	
B1 (inflammatory)	0 (0.00)
B2 (stricturing)	59 (26.9)
B3 (penetrating)	160 (73.1)
Disease duration, years	2.3 (0.8–4.9)
Endoscopic recurrence	135 (61.6)
Received therapy	
Thiopurine	64 (29.2)
Anti-TNF agents	110 (50.2)
Others	45 (20.5)

TNF, tumor necrosis factor.

40% of patients with endoscopic remission at 6 months postoperatively recurred after 14 months.[21] For this reason, postoperative patients should undergo colonoscopy every 1–2 years. These strategies significantly increase the patient burden and decrease patient compliance.

Patients with CD undergoing surgery may develop complications such as bile acid diarrhea, fat malabsorption, and small intestinal bacterial overgrowth, leading to symptoms that interfere with Crohn's disease activity index (CDAI) and make clinical symptoms unreliable.[8] The discordance between clinical and endoscopic manifestation was demonstrated in the PREVENT trial.
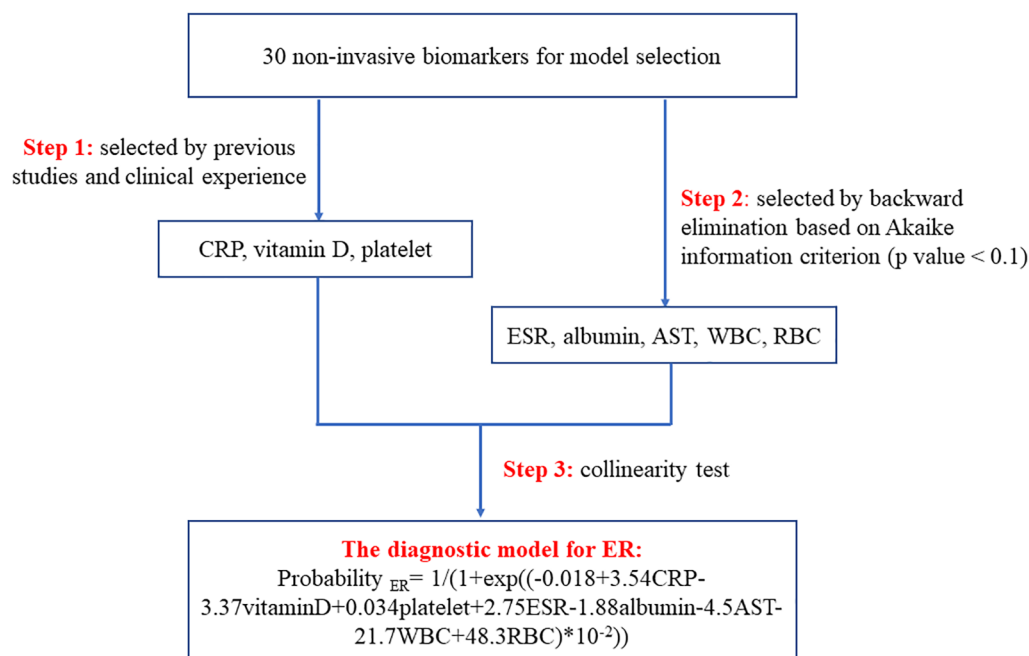
Figure 2. The predictor selection and algorithm for the endoscopic recurrence diagnostic model. AST, aspartate aminotransferase; CRP, c-reactive protein; ER, endoscopic recurrence; ESR, erythrocyte sedimentation rate; RBC, red blood cells; WBC, white blood cells.

Table 2. Final multivariate logistic regression model for identifying endoscopic recurrence.

	β coefficient, ($\times 10^{-2}$)	Odds ratio (95% CI)
Intercept	−0.018	
CRP (mg/L)	3.54	1.04 (1.00–1.08)
Vitamin D (mg/L)	−3.37	0.97 (0.92-1.02)
Platelets ($\times 10^9$/L)	0.334	1.00 (1.00–1.01)
ESR (mm/h)	2.75	1.03 (1.01–1.05)
Albumin (g/L)	−1.88	0.98 (0.90–1.06)
AST (U/L)	−4.50	0.96 (0.92–0.99)
WBC ($\times 10^9$/L)	−21.7	1.62 (1.00–2.68)
RBC ($\times 10^{12}$/L)	48.3	0.80 (0.66–0.97)

AST, aspartate aminotransferase; CI, confidence interval; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; RBC, red blood cell; WBC, white blood cell.

Patients with active clinical symptoms (CDAI > 150) had a sensitivity of only 66.7% and a specificity of 45.5% for predicting endoscopic disease activity.[22] Therefore, early endoscopy within 6 months after surgery and adjusting treatment accordingly may improve outcomes compared with relying on symptoms alone.
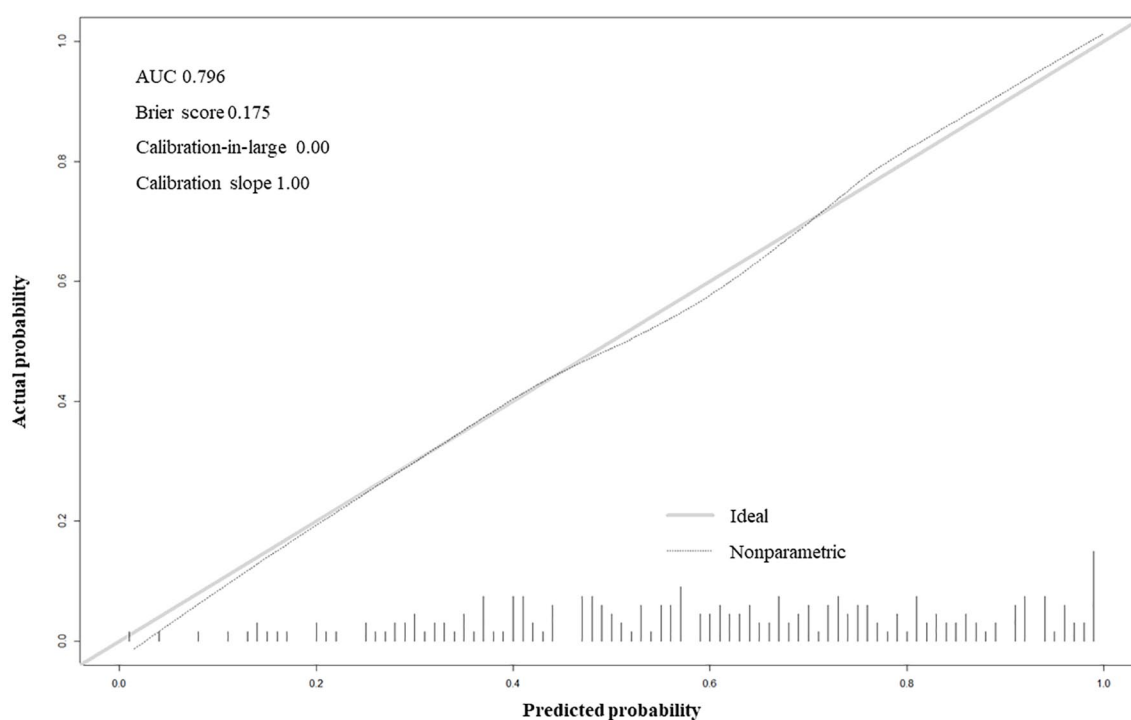
Fecal biomarkers such as calprotectin have been evaluated for predicting postoperative recurrence. When predicting postoperative recurrence, fecal calprotectin showed different sensitivities (16–95%), specificities (45.9–97%), and cutoff values (60–274 µg/g) in different studies, while lactoferrin and S100A12 seemed to show little value in a few studies.[19,23] Single serum/plasma markers indicating systemic inflammation show low sensitivity in revealing postoperative recurrence. The endoscopic healing index (EHI), a series of serum biomarkers that can reflect endoscopic inflammation, shows similar efficiency to fecal calprotectin.[23] Other new indicators such as microbiota and serum oncostatin M have recently been found to identify postoperative recurrence, but their efficacy still needs to be proven.[24,25] Overall, clinical symptoms, single stool, and serum/plasma biomarkers have limited efficiency in identifying postoperative recurrence.

For these reasons, validated, non-invasive biomarkers to identify recurrence in CD patients

Table 3. The discriminatory ability of the diagnostic model in identifying endoscopic recurrence.

	AUC (95% CI)	Cutoff value	Sensitivity	Specificity
Appearance performance	0.796 (0.737–0.855)	0.593	0.733	0.750
Internal validation[a]	0.781 (0.780–0.782)	0.655 (0.651–0.659)	0.647 (0.643–0.651)	0.811 (0.807–0.815)

AUC, area under the characteristic curve; CI, confidence interval.
[a]The mean (95% CI) of AUC – cutoff values – sensitivity and specificity in internal validation was calculated by bootstrapping procedure with 1000 replications.

AUC 0.796
Brier score 0.175
Calibration-in-large 0.00
Calibration slope 1.00

— Ideal
...... Nonparametric

Figure 3. The calibration ability of the diagnostic model to distinguish between endoscopic recurrence and endoscopic remission.

help improve postoperative patient management and limit invasive procedures. Our group developed a multivariate logistic regression model containing CRP, vitamin D, platelets, ESR, albumin, AST, WBC, and RBC to identify postoperative relapse in CD patients. It had a relatively high efficiency with a mean and 95% CI of 0.781 (0.780–0.782), 0.647 (0.643–0.651), and 0.811 (0.807–0.815) for AUC, sensitivity, and specificity, respectively. These indicators in the model are readily available in clinical practice, even in community hospitals, through simple blood tests. These features are critical to reducing patient burden and improving patient compliance.

However, this study also has some limitations. First, external validation of the diagnostic model was not performed due to the limited sample sizes. Since only internal validation was done in our study, a large multicenter study would be needed to confirm the predictive power and generalizability of the model. In addition, this study is retrospective and we did not directly compare the predictive power of the diagnostic model with that of fecal calprotectin, the most commonly used fecal biomarkers to monitor CD disease activity. A recent meta-analysis showed that fecal calprotectin with a cutoff value of 50–150 µg/g had relatively high sensitivity but poor specificity

for identifying endoscopic recurrence.[26] However, the diagnostic model in this study had a high specificity for identifying endoscopic recurrence, so there is interest in combining fecal calprotectin with a diagnostic model that may improve the predictive ability for endoscopic recurrence, which requires further study. Third, only patients with a history of ileocolonic resection were recruited for this study, so it is unclear whether this diagnostic model would be helpful in patients with colon resection or ileostomy ileocolic resection. Furthermore, disease activity on deep ileum and jejunum were not evaluated in our study, because the endoscopic recurrence was assessed based on the Rutgeerts score. Therefore, whether our diagnostic model can assess the endoscopic activity of upper gastrointestinal tract in postoperative CD patients was not clear.

In conclusion, we have developed and validated a promising diagnostic model for identifying endoscopic recurrence in patients after CD surgery. This diagnostic model can be easily applied to clinical practice and helps to monitor endoscopic recurrence, which is vital for treatment selection.

Author contributions

Gaoshi Zhou: Data curation; Formal analysis; Investigation; Methodology; Writing – original draft.

Rirong Chen: Data curation; Formal analysis; Investigation; Methodology; Project administration; Software.

Yueyun Jiang: Data curation; Investigation; Methodology; Project administration.

Li Li: Data curation; Formal analysis; Methodology; Resources; Validation.

Jieqi Zheng: Investigation; Methodology; Resources; Software.

Chao Li: Methodology; Project administration; Software.

Shenghong Zhang: Conceptualization; Funding acquisition; Supervision; Writing – review & editing.

Minhu Chen: Conceptualization; Funding acquisition; Supervision; Writing – review & editing.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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